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## Serological subsets of Juvenile Idiopathic Inflammatory myopathies - an update

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Abstract: (120 words max)

In this review we explore the different characteristics of the serological phenotypes identified in juvenile-onset myositis and consider how the serological sub-classification of patients with juvenile myositis can be advantageous both in terms of reaching what can be a difficult diagnosis and informing on prognosis. Recent studies have described the autoantibody associated disease phenotypes and outcome for those with juvenile-onset disease and include analyses of large juvenile-onset myositis cohorts. Here we describe the autoantibody associated disease features for patients within juvenile-onset myositis in detail and discuss the expanding opportunities and strategies for myositis specific autoantibody testing in clinical practice.

Keywords:

Autoantibody

Myositis

Juvenile

Phenotype

Muscle disease



### The idiopathic inflammatory myopathies and juvenile onset disease

The idiopathic inflammatory myopathies are a group of autoimmune chronic inflammatory muscle disorders characterised by muscle inflammation or 'myositis'. Juvenile-onset (JIIM) is typically defined as an age of onset below 16 years of age (or 18 years in the US and Canada) and dermatomyositis (JDM) is by far the most common sub-type. Dermatomyositis also affects the skin producing a variety of characteristic cutaneous features: These include erythematous or purple spots on bony prominences, especially the knuckles, which are known as Gottron's papules in addition to purplish discolouration and swelling around the eyes. The latter is described as heliotrope, as it resembles in colour heliotrope flowers, which have small purple petals. Erythematous patches can occur, typically on sun exposed areas including the nose, cheeks and elbows in addition to the more classical shawl sign across the shoulders and v-sign on the upper chest. . Ragged cuticles and nail fold erythema is common. Other accepted JIIM subtypes include polymyositis (distinguished from dermatomyositis by a lack of skin disease in addition to specific histological features on muscle biopsy), myositis overlap with other connective tissue diseases and amyopathic dermatomyositis where paradoxically there is an absence of muscle involvement but the presence of pathognomonic cutaneous lesions. Inclusion body myositis does not occur in children.

The presenting features of JIIM are variable however skin disease, weakness and systemic features, such as fever, fatigue and weight loss are reported in the majority of patients.(1) Weakness is typically progressive and in some cases can become profound. Age at disease onset can be an important differentiating factor between myositis subgroups; both juvenile polymyositis and juvenile myositis overlap typically occur in older children compared to juvenile dermatomyositis which has a median age at onset of 6.9 years.(2)

JIIIM are very rare diseases; the incidence varies depending on the population studied but is estimated to be just 2-4 per million children.(3, 4) Skin disease occurs in more than 95% of children with JIIM and

as such is a key diagnostic feature. Unfortunately, while the hallmark cutaneous features of dermatomyositis are well described in the literature, in reality diagnosis is often less straightforward: The rash of juvenile dermatomyositis can be subtle or atypical, and particularly in the absence of muscle disease may be confused with more common dermatological conditions such as psoriasis. The rarity of JIIM, combined with disease variability and potentially subtle disease-specific examination findings can lead to diagnostic delay.

#### Disease variability and features of severe disease

JIIM is a heterogeneous disease with varied clinical manifestations even within the dermatomyositis subgroup. Clinical outcome is highly variable and ranges from a relatively mild disease responsive to immunosuppressive treatment, to that causing significant morbidity and mortality. In the pre-steroid era, in the absence of any available treatment, approximately one third of children with JIIM would die, one third would recover and one third would be expected to survive but with significant residual disability.(5, 6) Although modern treatment has dramatically improved patient outcomes, and overall mortality has been reduced to 3-4% (5, 7) the standardised mortality ratio for children with JIIM remains considerably higher than all other paediatric rheumatological diseases, except lupus.(8) Furthermore, long-term outcome studies demonstrate a considerable number of patients with ongoing disease or damage (5, 9) in addition to ongoing active disease in over half of patients on prolonged follow-up.(10) Inadequate or delayed treatment has been shown to be an important factor in predicting a chronic course and poor outcome, and several studies have suggested that early aggressive treatment results in reduced morbidity and improved outcome. (11-13) In addition to strategies to facilitate the early diagnosis and treatment of patients with JIIM prognostic factors are also needed to identify those patients at greatest risk of both mortality and long-term morbidity.

A recent study investigating mortality in JIIM identified the clinical subgroup (higher risk of death in JIIM-connective tissue disease overlap and juvenile polymyositis) and disease severity at onset as predictors of mortality.(7) As with most studies in JIIM numbers were limited and so it remains possible that other variables analysed, which lost significance in multivariate analysis, may also be important. It is noteworthy that seven out of 17 patients died from pulmonary causes, predominantly interstitial lung disease (ILD). We know that ILD is a significant cause of mortality in adults-onset myositis associated with a poorer prognosis.(7, 14, 15) In a smaller, single-centre study of JIIM mortality in India, ILD was similarly implicated in three out of five deaths.(16) In Caucasian populations the incidence of ILD in JIIM has been reported to be in the region of 5% (2, 17) but appears to be higher (12%) in other ethnic groups.(18) It is important that patients at risk of ILD are identified early for appropriate monitoring and aggressive management.

Whilst with modern treatment regimens mortality in JIIM is fortunately low, there remain many patients who respond sub-optimally with ongoing active disease, organ damage and poor quality of life. The ability to identify early those patients likely to develop features such as calcinosis, vasculopathy and lipodystrophy is highly desirable. These complications are not uncommon; calcinosis (the deposition of insoluble calcium in the skin and subcutaneous tissues) occurs in approximately one third of affected children.(19) It is a cause of considerable morbidity, and can lead to skin ulceration, pain from nerve entrapment and joint contractures.(1, 9, 20) Lipodystrophy affects 10-40% of children with myositis and in addition to changes in physical appearance is associated with metabolic abnormalities and insulin resistance.(21) The long-term implications of these metabolic abnormalities are not yet clear.

#### Myositis specific and associated autoantibodies and serological subsets of myositis

The identification of disease specific autoantibodies are a useful tool in the diagnosis of many rheumatological disorders. Myositis specific autoantibodies (MSA), are a collection of autoantibodies directed against intracellular antigens exclusively found in patients with idiopathic inflammatory myopathies. Myositis associated autoantibodies (MAA) can be identified in patients with myositis and other associated connective tissue disorders. MSA are typically found in isolation but the identification of a less-specific MAA e.g. anti-Ro52 does not preclude the presence of an MSA. MSA and/or MAA can now be identified in 60% of children with myositis (22)(personal data). Furthermore, sub-dividing myositis patients by MSA type identifies distinct clinical subsets of myositis and can predict the likelihood of important disease complications. (22, 23) For a summary of autoantibody associated clinical features see Table 1.

The same autoantibodies are seen in both adult and juvenile forms of myositis, and associations between HLA risk alleles and autoantibody subgroups are common across the age range, suggesting similarities in the underlying pathogenesis. The frequency of MSA sub-groups however varies between adult and juvenile disease and the population studied. The specific disease phenotype for autoantibody subgroups also varies depending on the population studied and between adults, children and even young adults. It remains unclear whether these autoantibodies themselves contribute to pathology and if so, how age and ethnic background/ environmental specific effects are mediated.

#### 'Classic' Myositis Specific Autoantibodies in juvenile myositis

Traditional MSA, that is those proposed by Love *et al.* in 1991 as a means of subdividing patients with myositis into homogenous subgroups, are now well described and can be routinely tested for in many hospital laboratories.(24) Unfortunately, these autoantibodies are only rarely found in those with JIIM; individually occurring in less than 5% and collectively in approximately 10% of affected children.(25)



### *Anti-Mi2 autoantibodies*

Anti-Mi2 is the archetypal dermatomyositis autoantibody but can be identified in just 3-10% of those with juvenile-onset disease.(25-27) Affected patients typically present with hallmark rashes of dermatomyositis in addition to proximal muscle weakness. While this group typically have a higher creatinine kinase (25) and higher muscle biopsy scores indicating of more severe histopathological disease, they appear to be treatment sensitive and are more likely to be in remission and off medication at 2 years post-diagnosis.(28) This is supported by an earlier study of Argentinian patients by *Espada et al.* who also noted that patients with anti-Mi2 were more likely to have a benign course.(29)

### *Anti-synthetase autoantibodies*

Autoantibodies targeting aminoacyl- tRNA synthetases (anti-Jo-1, anti-PL12, anti-PL7, anti-OJ, anti-EJ, anti-KS, anti-Zo and anti-Ha) can collectively be identified in less than 5% of children. Juvenile patients with anti-synthetase autoantibodies tend to be older at disease onset.(25) As in adult onset disease anti-Jo-1 is the most common anti-synthetase autoantibody identified and the clinical phenotype where described is similar to the classic 'antisynthetase syndrome' described in adult patients; consisting of fever, myositis, arthritis, Raynaud's phenomenon, mechanics hands and interstitial lung disease (ILD).(25, 30) Patients with an anti-synthetase autoantibody can be expected to have a chronic continuous disease course and mortality is highest in this autoantibody group at 17%; primarily due to the development of ILD.(25)

### *Anti-SRP autoantibodies*

Anti-SRP autoantibodies are associated with necrotising autoimmune myositis. Similarly to affected adults juvenile patients with anti-SRP typically have polymyositis (i.e. no rash) with profound muscle weakness and high CK levels. ILD and cardiac involvement have also been described in the context of

juvenile-onset disease.(25, 31) Juvenile patients with anti-SRP are more likely to be older (median age 15 years) and are mostly females of black ethnicity.(25)

#### 'New' Myositis Specific Autoantibodies in juvenile myositis

It is only since discovery of several further MSA that serological subgrouping of patients with JIIM has truly become possible. Whilst not yet routinely tested for by many centres the addition of these 'new' MSA enables an autoantibody to be detected in more than 60% of those with JIIM.(25)(personal data) Recent work exploring the clinical phenotype associated with these new MSA subgroups has emphasised the clinical diversity within JIIM and highlighted the potential clinical utility of subgrouping patients by serological profile. It is important to note that whilst there is a strong association between some of these newer MSA and malignancy in adult myositis populations, namely anti-TIF1 $\gamma$  and anti-NXP2, this association has not been observed in those with juvenile-onset disease, or indeed young adults.(32, 33)

#### *Anti-TIF1 $\gamma$ autoantibodies*

Autoantibodies to a 155/140kDa doublet, subsequently discovered to target the transcription factor TIF1 $\gamma$ , have been identified in 22-36% of juvenile myositis patients.(29, 32, 34, 35) They are associated with more severe cutaneous disease and several hallmark dermatomyositis skin lesions including Gottron's papules, shawl sign and v-sign have been described to occur with greater frequency in this patient group.(25, 35) While in juvenile patient populations no autoantibody specific cutaneous features have been described, in adults with anti-TIF1 $\gamma$  characteristic 'red and white' lesions were recently reported and it was noted that in general DM rashes in patients with anti-TIF1 $\gamma$  were more likely to occur in a photo-exposed pattern.(36) This is an interesting observation given that that juvenile patients with a higher historical UV exposure in the month prior to diagnosis have been shown to be at higher risk of having anti-TIF1 $\gamma$  antibodies.(37) UV exposure may therefore have a role to play in the pathogenesis of myositis or at in least certain subgroups.

Anti-TIF1  $\gamma$  in adult patients may be associated with lesser degrees of muscle weakness: *Fujimoto et al.* reported that 32% of their anti-TIF1 $\gamma$  cohort presented with clinically amyopathic disease and while *Fiorentino et al.* did not find clinically amyopathic dermatomyositis to be more common in those with anti-TIF1 $\gamma$  they did report lower mean levels of muscle enzymes.(32, 36) This has not been found in juvenile cohorts, however and in contrast *Gunawardena et al.* identified a trend towards lower childhood myositis scores in those with anti-TIF1 $\gamma$ , corresponding to greater weakness, although this did not reach statistical significance.(35)

Lipodystrophy has also been associated with anti-TIF1 $\gamma$  in patients with juvenile-onset myositis.(21, 25) Lipodystrophy is a late complication of JIIM and is associated with more severe chronic disease. In patients with generalised or partial lipodystrophy there are often associated metabolic abnormalities including insulin resistance, diabetes mellitus and hypertriglyceridaemia.(21) In a US JIIM cohort 28 patients (8%) were identified with associated lipodystrophy. It was noted that 86% of patients with generalised lipodystrophy had an anti-TIF1 $\gamma$  antibodies compared to 36% of the whole cohort.(21)

#### *Anti-NXP2 autoantibodies*

Anti-NXP2 autoantibodies (also termed anti-p140, P140 or anti-MJ) can be identified in 20-25% of juvenile cohorts and form a further major juvenile disease serological subgroup.(19, 25, 29) Anti-NXP2 autoantibodies are associated with several features of severe disease including calcinosis, a greater degree of muscle weakness (19, 25) and in a large US cohort an increased frequency of gastrointestinal bleeding, ulcers and dysphagia.(25) Disease outcome may be worse in this group as anti-NXP2 autoantibodies have been associated with more persistent disease activity and a worse functional status.(19, 25, 29) *Rider et al.* found that although mortality and severity of disease onset in this group was low, hospitalisation was common.(25)

### *Anti-MDA5 autoantibodies*

Anti-MDA5 autoantibodies target another 140kDa protein; Melanoma Differentiation Associated-gene 5. Initially termed anti-CADM140, they were first identified in adult Japanese patients with clinically amyopathic dermatomyositis and interstitial lung disease (ILD); a myositis phenotype common in East Asia.(22, 38, 39) Subsequently *Kobayashi et al.* in a small study of Japanese JIIM patients also revealed a high proportion (38%) with anti-MDA5.(40) All of these patients had had ILD and three patients, with very high titres of anti-MDA5, had rapidly progressive ILD.(40) In a recent study *Kobayashi et al.* describe the clinical and laboratory features of 10 Japanese JIIM patients with rapidly progressive ILD. All patients of these patients were found to have anti-MDA5; two presented with clinically amyopathic disease and the remaining eight had muscle weakness. Importantly four patients had no respiratory symptoms or signs of ILD at the time of diagnosis. Seven patients (70%) died, despite intensive treatment and lung histopathology following biopsy or autopsy was compatible with diffuse alveolar damage. Other groups included in this study were 14 juvenile-myositis patients with chronic ILD (10 of whom were found to have anti-MDA5) and 22 patients without ILD (none of whom were found to have anti-MDA5). While rapidly progressive ILD is a major cause of death in JIIM in Japan (41) this is not the case in other patient groups; in Caucasian populations, while data is limited, ILD is perceived to be rare and the incidence has been reported to be in the region of 5%. (2, 17)

We identified anti-MDA5 in a much smaller proportion of our UK JIIM patient population (7%) than has been described in East Asian JIIM patient cohorts.(42) The clinical phenotype of UK JIIM patients with anti-MDA5 was similar to that described in US adult patient cohorts with less muscle involvement, an increased risk of ILD (but not rapidly progressive ILD) and associations with arthritis and both skin and oral ulceration.(42-44) In striking contrast to East Asian populations and despite significant associations with both ILD and ulceration, both considered to be severe disease manifestations of JIIM, this group appeared to do well and were more likely to enter disease

remission.(42) In some respects this is not surprising as current definitions of remission focus heavily on evidence of muscle involvement, which is less prominent in this group from the outset, and can consequently underestimate ongoing disease activity in other areas.(45) Our patients with anti-MDA5 and associated ILD, however, did respond well to conventional therapy.(42)

For patients with JIIM and anti-MDA5 the differences between populations in both clinical presentation and prognosis is striking. This may be due to differences in genetic background, environmental influences or a combination of both. The human leukocyte antigen (HLA) system confers susceptibility to a variety of autoimmune disease and is the major genetic region associated with IIM.(46) HLA genotype also predicts which MSA and hence which clinical phenotype an individual is most likely develop. HLADRB1\*0101/\*0405 has been associated with anti-MDA5 in a Japanese population but genetic susceptibility to anti-MDA5 associated IIM in other populations has not been reported.(47) In adult IIM differences in both the prevalence and the clinical associations of anti-MDA5 have been identified between Chinese and Japanese patient groups; populations that had previously been considered similar.(48) While genetic differences were not specifically examined the authors postulated that the combined allele frequency of HLADRB1\*0101 and \*0405 may be a contributory factor, as these have been shown to be remarkably different between Japanese and Chinese populations.(48) Evidence for external factors influencing myositis phenotype comes from Japan, where the relative prevalence of anti-MDA5 associated myositis has been shown to be increasing and to be higher in rural areas.(49) It seems feasible that an individual's genetic background along with different environmental triggers may influence both the predisposition to myositis sub-types and the severity of key disease features like ILD.

#### *Other MSA in juvenile idiopathic inflammatory myopathies*

Other known MSA are very rare in juvenile-onset disease and where described the associated phenotypes appear to be similar adult patients. Anti-HMGCR have been described in adult patients with necrotising autoimmune myopathy and are associated with statin use, although 40-70% of

patients have no history of statin exposure.(50, 51) They have also been identified in a small number of JIIM patients.(50, 51) A cohort of 183 French patients suspected of having necrotising autoimmune myopathy on the basis clinical and/or pathological criteria included eight juvenile-onset patients. All eight cases were found to be positive for anti-HMGCR (seven patients were aged >16 years at the time of testing).(50) Interestingly, while four patients were diagnosed at the outset with an inflammatory myopathy, in view of rapidly progressive weakness and high creatinine kinase levels, the remaining four were initially diagnosed as having limb girdle muscular dystrophy because of slowly progressive weakness, thus highlighting one of the potential diagnostic benefits of MSA testing.(50)

Anti-SAE has been described in a handful of juvenile cases worldwide and knowledge of the associated clinical phenotype is therefore extremely limited. (2, 52) To the best of our knowledge all cases have been in children with dermatomyositis suggesting similarities to adult-onset disease, where patients were described to initially present with clinically amyopathic myositis but subsequently develop muscle involvement.(53)

#### Myositis Associated Autoantibodies in juvenile myositis

*Rider et al.* identified a myositis associated autoantibody (MAA) in just under 16% of children with JIIM.(25) Anti-Ro52, anti-U1-RNP and anti-PmScl were the most frequent; each identified in 4-6%. This group of autoantibodies were commonly identified in conjunction with an MSA and it is important to note that the presence of an MAA, particularly anti-Ro52 which in adults can be identified in conjunction with anti-Jo-1 in more than 50% of cases, should not prevent additional further investigations for MSA.(25, 54) Whilst numbers were insufficient to analyse the phenotype in any detail these autoantibodies are all more commonly identified in those patients classified as myositis-connective tissue disease overlap.(2)

#### Testing for autoantibodies in juvenile dermatomyositis progress and pitfalls

Despite the fact that the so called 'new' MSA were first appreciated to be common and clinically relevant to JIIM between five and ten years ago, testing for these autoantibodies is not yet standard clinical practice. This is in part due to difficulties with testing methodology: Standard immunological techniques to detect autoantibodies such as indirect immunofluorescence of Hep-2 cells can identify a positive antinuclear antibody (ANA) in the majority of children with JDM (>70%),<sup>(2, 26)</sup> however whilst this may help to distinguish a child with an inflammatory myopathy from one with a non-immune myopathy or muscular dystrophy, it provides neither a diagnostic nor a prognostic result. Furthermore, a negative ANA result does not preclude the presence of a MSA; many of which produce cytoplasmic staining patterns and the identification of a MAA such as anti-Ro52, (commonly included on a standard extractable nuclear antigens (ENA) screening panel) does not preclude the presence of a more specific MSA not otherwise tested for. Whilst a low titre homogenous ANA and a speckled or reticular pattern has been described in conjunction with anti-TIF1 $\gamma$  and anti-MDA5 autoantibodies respectively, these are non-specific findings that have been inconsistently reported. (34, 39, 42, 55) In contrast, both anti-synthetase and anti-SRP autoantibodies should be expected to produce cytoplasmic staining and a homogenous-nucleolar staining pattern on immunofluorescence in a patient with suspected myositis should raise suspicion for anti-PmScl. However, these are all uncommon autoantibodies in JIIM and cytoplasmic staining may not be routinely reported.

In brief, using standard screening techniques employed in most hospital laboratories neither a positive nor a negative ANA and/or negative ENA result preclude the presence of MSA in patients with myositis or CTD-myositis overlap. In addition, while many hospital laboratories do have the ability to detect classic MSA such as anti-Mi2 and anti-Jo-1 and the ANA pattern can provide important clues to the presence of the other anti-synthetases, anti-PmScl and anti-SRP these autoantibodies are all rarely found in those with JIIM.

Immunoprecipitation is generally considered the gold standard method for MSA detection but this is costly, low-throughput and available in a limited number of centres worldwide. As such, there has been a significant interest testing for specific MSA using techniques that could be employed in the routine laboratory setting, with numerous publications.(56-63) In addition to the development of specific testing methodologies to detect a number of the new MSA (56, 57, 60-62) multiplex assays have also been designed which have the advantage of being able to detect many specific autoantibodies in a single run.(58, 59, 63) This type of assay provides the opportunity to save time in addition to materials and labour costs. A significant limitation of the clinical utility of autoantibodies in patients with JIIM has been the availability of testing and the development of these assays is an exciting step.

Several kits are now commercially available that include autoantibodies of relevance in JIIM, however, it remains important to ensure that they are appropriately validated. In our experience predominantly false positive but also false negative results can be problematic. Unfortunately, there are as yet no reports directly comparing the sensitivity and specificity of results obtained from different types of assays or from different manufacturers. For JIIM it is particularly important accurate results for the most commonly identified MSA can be identified and as these are 'newer' assays less is known of their reliability. These problems are further compounded by the rarity of IIM and JIIM and the consequent low numbers of samples that are typically processed by an individual laboratory.

Furthermore, as a specific panel of autoantibodies are tested for clinicians must be aware of what is and is not included. Ensuring the ANA pattern on immunofluorescence is consistent with the autoantibody result obtained can be helpful in identifying potential false positive or otherwise erroneous results. See Figure 1 for an overview of autoantibody testing approaches in JIIM.

#### MSA titre and autoantibody persistence

The development of quantitative techniques such as ELISA to detect autoantibodies in myositis has led to a growing interest in the potential clinical utility of autoantibody titre to predict disease activity



and response to treatment. To date little is understood about the clinical implications of autoantibody titre in myositis, particularly in juvenile disease. In adults, small studies have shown a relationship between the titres of anti-Jo-1, anti-MDA5, anti-HMGCR and anti-SRP autoantibodies with disease activity measures. (64-68) In addition, the titre of anti-MDA5 has been shown to be useful in predicting response to treatment in Japanese children with JIIM. (69, 70) In a small pilot study we were able to demonstrate variability in anti-TIF1 $\gamma$ , anti-NXP2 and anti-MDA5 titre over time in children with JIIM. The disappearance of autoantibodies between first and last available samples was common and antibody titres correlated with physician global assessment score. (71) Variability in autoantibody titre over time may have implications for determining autoantibody frequency if post-treatment samples are used for analysis. *Sato et al.* previously demonstrated a fall in anti-MDA5 titre in response to treatment and our results suggest that this also applies to other MSA subgroups common in JIIM. (72) Some apparently 'autoantibody negative' patients may therefore be patients whose antibody titre has subsequently become undetectable following treatment. This has implications for determining autoantibody prevalence and phenotype associations within JIIM as a whole. Further work is needed with larger patient numbers to confirm preliminary results and crucially to assess whether alterations in autoantibody titre pre-date changes in disease activity, a fundamental feature of any predictive biomarker.

#### Expert Commentary:

Juvenile idiopathic inflammatory myopathies are heterogeneous and challenging diseases. MSA provide a unique opportunity to subdivide patients into distinct and clinically homogenous subgroups following a simple blood test. To the clinician this provides an opportunity to confirm what at times can be a difficult diagnosis, particularly for the non-specialist and to facilitate a strategy for further investigation, treatment and monitoring. For the patient and their parents this can also help to provide diagnostic clarity and inform on prognosis and outcome. In the past the

prospect of identifying an MSA in JIIM was extremely limited however with the identification of the newer MSA and the characterisation of their associated phenotypes, this is now feasible for the majority patients.

#### Five year review:

The recent availability of multiplex assays with the ability to screen for MSA common to JIIM is an exciting development that opens the door to the use of MSA as a diagnostic and prognostic tool in juvenile-onset disease. It seems likely that in the near future these assays will become routinely used to confirm a diagnosis of JIIM and to help identify myositis in children presenting as more of a diagnostic challenge, for example those with clinically amyopathic disease. This may well follow-on to changes to current accepted diagnostic criteria. MSA will also guide strategic further investigation and for example we would anticipate a low threshold for high resolution CT scanning in children found to have an anti-synthetase autoantibody or anti-MDA5. Further work is needed on prospectively collected serial samples to clarify the potential utility of autoantibody titres in disease monitoring but it seems likely that, at least for certain MSA, autoantibody titre could become a useful clinical tool, perhaps akin to dsDNA monitoring in patients with lupus.

In the longer-term, given the significant clinical differences between the autoantibody subgroups it might be anticipated that patients would benefit from different treatment approaches. The evidence base for treatment of JIIM is extremely limited but while there is no accepted standardised treatment regimen, corticosteroids plus additional immunosuppressive agents form the mainstay of treatment. One difficulty in treating patients with JIIM is judging the severity of disease accurately, as under-treatment can increase the risk of long-term disability.<sup>(11-13)</sup> While as yet there is no clear evidence or guidelines to recommend a differential treatment approach for JIIM serological subgroups it is becoming clear that MSA can help to predict disease severity and clinical course, <sup>(19, 28, 42)</sup> which thus has the potential to influence treatment decisions both in terms of the aggressiveness of the

initial treatment approach and when to reduce and/or stop medication. There is also emerging evidence of a differential treatment response to certain medications by MSA subgroups.(73) Further work is needed to confirm this and we may therefore begin to see more clinical trials subdividing patients by autoantibody status to assess the differential effects of an intervention or treatment. This should ultimately lead on to patient centred treatment that considers MSA status as a key influence in regimen choice.

Key points:

1. Juvenile myositis is characterised by muscle inflammation with associated weakness.
2. >95% of those affected have associated pathognomonic skin changes and fit into the dermatomyositis subgroup
3. Despite the description of hallmark cutaneous features diagnosis is difficult in part due to disease rarity and heterogeneity
4. Modern immunosuppressive treatments have improved disease outcome but many children continue to suffer from ongoing chronic disease and associated damage
5. Myositis specific autoantibodies are found exclusively in patients with myositis and have diagnostic value
6. Myositis specific and associated autoantibodies can be used to subdivide juvenile onset myositis patients into clinically homogenous sub-groups and inform prognosis
7. The most common autoantibodies identified in juvenile myositis are anti-TIF1 $\gamma$ , anti-NXP2 and anti-MDA5
8. These autoantibodies are not detected as part of routine hospital laboratory screening methods although commercial assays are available
9. Specialised testing is currently only available at a limited number of centres worldwide

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Table 1. Myositis specific antibody phenotypes in juvenile-onset myositis

A description of the myositis specific autoantibody subgroups that can be identified in juvenile-onset myositis along with their frequency and key clinical features

	Autoantibody frequency	Important clinical features	Outcome
<i>JDM overall</i>	<i>MSA can be identified in &gt;50% and MSA and/or MAA in &gt;60%</i>	<i>Muscle disease Cutaneous disease Calcinosis Vasculopathy Lipodystrophy Interstitial lung disease Gastrointestinal involvement</i>	<i>On long-term follow-up 40% have a reduced functional ability and 6% major impairment;(5) &gt;50% have ongoing disease activity.(10) Mortality is &lt;3%(5)</i>
Anti-Mi2	3-10%	Hallmark DM rash and muscle weakness.	Good response to treatment and benign clinical course(25, 28, 29)
Anti-tRNA synthetase	<5%	Anti-synthetase syndrome <sup>a</sup>	Significantly higher mortality, primarily due to ILD.(25)
Anti-SRP	<2%	No rash. Necrotising autoimmune myositis with severe weakness and very high CK.	High risk of hospitalisation. Chronic disease course with high level of wheel chair use.(25)
Anti-Tif1y	22-29%	Severe cutaneous disease & lipodystrophy (21, 35)	Low mortality. (25)
Anti-NXP2	20-25%	Severe weakness, calcinosis, gastrointestinal bleeding, dysphagia and ulcers (19, 25, 29, 74)	Persistent disease activity. Low mortality. Increased risk of hospitalisation.(25)
Anti-MDA5	7-38% <sup>b</sup>	CADM and RP-ILD in East Asian populations. Mild muscle disease, ulceration, arthritis and ILD in Caucasian populations. (40, 42)	High mortality in East Asian populations. Possibly better outcomes in Caucasians and more likely to enter disease remission.(40, 42)
Anti-HMGCR	unknown	Necrotising autoimmune myositis. (50)	unknown
Anti-SAE	<1%	May present as CADM the progress to muscle weakness	unknown

DM dermatomyositis, ILD interstitial lung disease, CK creatinine kinase, CADM clinically amyopathic dermatomyositis, RP-ILD rapidly

progressive interstitial lung disease

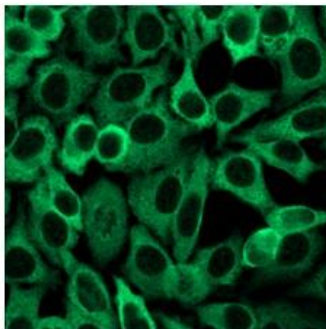
- a. Fever, myositis, arthritis, Raynaud's phenomenon, mechanics hands and interstitial lung disease
- b. Frequency appears to be population dependent. Anti-MDA5 is common in East Asian populations

Figure 1. Myositis specific autoantibody detection in juvenile-onset myositis

A summary of the standard methods for autoantibody detection along with their advantages and limitations in juvenile-onset myositis

### Routinely available tests

#### Indirect Immunofluorescence of Hep-2 cells



70% of JJIM are ANA positive.

The staining pattern is non-specific but can provide clues to autoantibody specificity.

Cytoplasmic staining due to anti-PL7 is shown here.

#### Extractable nuclear antigens (ENA)

Samples positive by immunofluorescence are typically examined for the presence of a standard panel of ENA.

Most commonly this will include MAA and possibly anti-Jo1. MSA commonly identified in JJIM are unlikely to be tested for routinely.

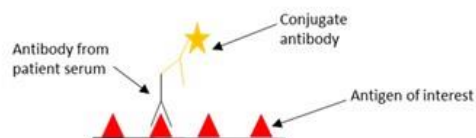
### Specialised and more specific tests

#### Tests for specific MSA

ELISA and immunoblot use immobilised recombinant antigen or antigens of interest and probe this with patient serum.

A panel of MSA can be tested for in this manner.

These assays are often sensitive but can suffer from problems with false positive results.



#### Immunoprecipitation

This method can detect novel autoantibodies.

It can be difficult to distinguish between autoantigens of similar molecular weights and additional confirmatory testing should be employed in such cases.

An Immunoprecipitation gel showing 5 lanes with bands at 155 and 140kDa consistent with anti-Tif1y. The 155 band is typically stronger than the 140 band.

